Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4978	paclitaxel	US-PGPUB; USPAT	OR	OFF	2004/10/08 16:03
L2	119	paclitaxel and design and (molecular adj modeling)	US-PGPUB; USPAT	OR	ON	2004/10/08 16:05
L3	339	paclitaxel and design and angstrom and side adj chain	US-PGPUB; USPAT	OR	ON	2004/10/08 16:12
L4	320	paclitaxel and modeling and angstrom and side adj chain	US-PGPUB; USPAT	OR	ON	2004/10/08 16:13
L5	2	4 not 3	US-PGPUB; USPAT	OR	ON	2004/10/08 16:12
L6	320	(paclitaxel or taxane) and modeling and angstrom and side adj chain	US-PGPUB; USPAT	OR	ON	2004/10/08 16:14
L7	350	(paclitaxel or taxane) and (design or modeling or synthesize) and angstrom and side adj chain	US-PGPUB; USPAT	OR	ON	2004/10/08 16:20
L8	1	(paclitaxel or taxane) and (design or modeling or synthesize) and angstrom and side and chain	EPO; JPO; DERWENT; IBM_TDB	OR	ON	2004/10/08 16:21
L9	1	(paclitaxel or taxane) and (design or modeling or synthesize) and angstrom	EPO; JPO; DERWENT; IBM_TDB	OR	ON	2004/10/08 16:21
L10	10	(paclitaxel or taxane) and (design or modeling or synthesize)	EPO; JPO; DERWENT; IBM_TDB	OR	ON	2004/10/08 16:21

US 20020028469A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0028469 A1**

Burch et al. (43) **Pub. Date: Mar. 7, 2002**

(54) **METHOD OF DEFINING GENUS OF CHEMICAL COMPOUND AND METHOD OF DESIGNING MOLECULES**

(76) Inventors: **Ronald M. Burch**, Wilton, CT (US); **Richard S. Sackler**, Greenwich, CT (US)

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(21) Appl. No.: **09/963,232**

(22) Filed: **Sep. 26, 2001**

Related U.S. Application Data

(63) Continuation of application No. 09/191,780, filed on Nov. 13, 1998, which is a non-provisional of provisional application No. 60/065,716, filed on Nov. 14, 1997.

Publication Classification

(51) **Int. Cl.**[7] **G01N 33/53**; C12P 21/04

(52) **U.S. Cl.** **435/7.1**; 435/70.21

(57) **ABSTRACT**

In accordance with an embodiment of the present invention, a method is provided for defining the portion of one or more chemical compounds having binding affinity for a target receptor. One or more chemical compounds to be tested are identified and then one or more key component fragments of the compound(s) are identified (e.g., a compound that "generically" defines the surface conformation and surface charge density of the one or more chemical compounds is "designed") which may impart affinity for the target receptor. Analogs containing one or more of the key component fragments are then identified or synthesized, and the analogs are coupled to a carrier to construct an analog-carrier conjugate. The analogs contain one or more functional groups such as carboxyl, hydroxyl, keto, amino, nitro, or sulfhydryl to react with the carrier molecule. Next, the analog-carrier conjugate is utilized to generate a panel of monoclonal antibodies in vivo or in vitro, wherein the monoclonal antibodies are capable of defining the characteristics of the key component fragments. Next, the monoclonal antibodies are assayed to determine which are most specific for the key component fragments of the chemical compound(s) and which bind to the chemical compound(s). Competitive binding assays, or other assays are then preferably conducted to determine the ability of the monoclonal antibodies to discriminate between different chemical compounds.

US006455575B2

(12) **United States Patent**
Golik et al.

(10) **Patent No.: US 6,455,575 B2**
(45) **Date of Patent: *Sep. 24, 2002**

(54) **PHOSPHONOOXYMETHYL ETHERS OF TAXANE DERIVATIVES**

(75) Inventors: **Jerzy Golik**, Southington; **Dolatrai Vyas**, Madison; **John J. Wright**, Guilford; **Henry Wong**, Durham; **John F. Kadow**, Wallingford, all of CT (US); **John K. Thottathil**, Robbinsville; **Wen-Sen Li**, Marlboro, both of NJ (US); **Murray A. Kaplan**, Syracuse; **Robert K. Perrone**, Liverpool, both of NY (US); **Mark D. Wittman**, Cheshire, CT (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/870,794**

(22) Filed: **Jun. 6, 1997**

Related U.S. Application Data

(63) Continuation of application No. 08/427,502, filed on Apr. 24, 1995, now abandoned, which is a division of application No. 08/245,119, filed on May 17, 1994, now abandoned, which is a continuation-in-part of application No. 08/154,840, filed on Nov. 24, 1993, now abandoned, which is a continuation-in-part of application No. 08/108,015, filed on Aug. 17, 1993, now abandoned, which is a continuation-in-part of application No. 07/996,455, filed on Dec. 24, 1992, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/337**; C07D 305/14
(52) **U.S. Cl.** **514/449**; 549/510; 549/511
(58) **Field of Search** 549/510, 511; 514/449

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Primary Examiner—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Samuel J. DuBoff; William T. Han

(57) **ABSTRACT**

The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

38 Claims, No Drawings

US005416225A

United States Patent [19]

Danishefsky et al.

[11] **Patent Number: 5,416,225**

[45] **Date of Patent: May 16, 1995**

[54] **TOTAL SYNTHESIS OF TAXOL**

[75] Inventors: **Samuel J. Danishefsky**, New Haven, Conn.; **William G. Bornmann; Yves Queneau; Thomas V. Magee**, all of New York, N.Y.; **Walter J. Krol**, Wallingford, Conn.

[73] Assignee: **Sloan-Kettering Institute for Cancer Research**, New York, N.Y.

[21] Appl. No.: **860,792**

[22] Filed: **Mar. 30, 1992**

[51] **Int. Cl.**[6] **C07D 317/72**

[52] **U.S. Cl.** **549/341**; 549/342

[58] **Field of Search** 549/341, 342

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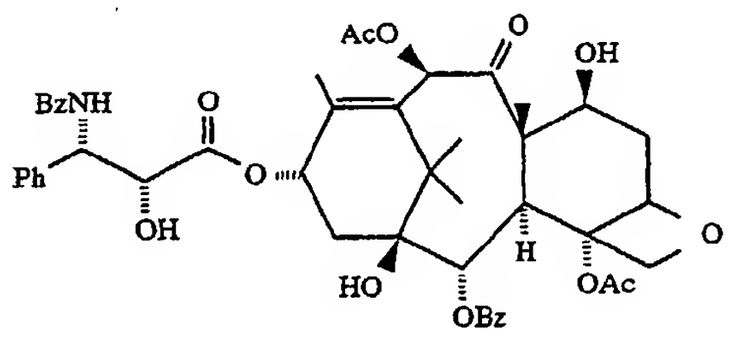
Primary Examiner—C. Warren Ivy
Assistant Examiner—Ba K. Trinh
Attorney, Agent, or Firm—John P. White

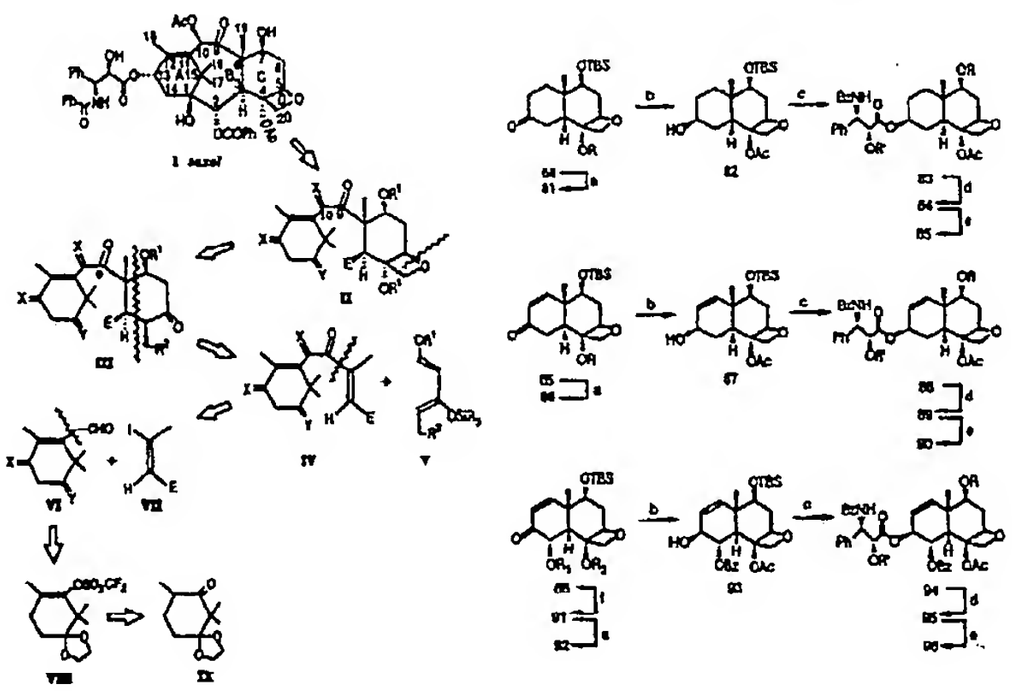
[57] **ABSTRACT**

The present invention provides two basic routes for the total synthesis of taxol having the structure:



The present invention also provides the intermediates produced in the above processes, processes for synthesizing these intermediates as well as analogs to taxol. Both the intermediates and analogs to taxol may prove to be valuable anticancer agents.

3 Claims, 20 Drawing Sheets



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3	X		WO 200105779 A	20010125	90
4	X		WO 200074667 A	20001214	97
5	X		US 6191290 B	20010220	14
6	X		WO 9933462 A	19990708	18
7	X		US 6197981 B	20010306	11
8	X		US 5723634 A	19980303	24
9	X		EP 882231 B	20020717	5

	Title	Current OR	Current XRef
1	Jasmine keto ester derivatives and their use for promoting growth in plant cells		
2	Diazosulfide compound and application in plant cell		
3	Designing anti-tumor compositions uses a molecular		
4	Inhibiting or reducing growth of cell for treating cancer, comprising administering telomere damage-inducing agent and telomerase		
5	New soluble tumor-directed paclitaxel derivatives are useful in the treatment of breast and ovarian cancer		
6	New paclitaxel analogs as anticancer drugs or intermediates for anticancer		
7	Taxol and derivatives produced synthetically - from 9-di:hydro-13-acetylbaccatin III increases availability of anti-tumour compounds		
8	New metal alkoxide compounds - useful for the synthesis of antitumour isoserine ester(s) by reaction		
9	Production of taxane(s) having antitumour activity and used to treat poly-cystic kidney disease - by extraction of Coniferales tissues other than Taxus tissues and identification of sources of		

US006191290B1

(12) **United States Patent**
Safavy

(10) **Patent No.: US 6,191,290 B1**
(45) **Date of Patent: Feb. 20, 2001**

(54) **TAXANE DERIVATIVES FOR TARGETED THERAPY OF CANCER**

(75) Inventor: **Ahmad Safavy**, Birmingham, AL (US)

(73) Assignee: **UAB Research Foundation**, Birmingham, AL (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/510,896**

(22) Filed: **Feb. 23, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/121,642, filed on Feb. 24, 1999, now abandoned.

(51) **Int. Cl.**[7] **C07D 305/14**; A61K 31/337

(52) **U.S. Cl.** **549/510**; 549/511; 514/449

(58) **Field of Search** 514/449; 549/510, 549/511

(56) **References Cited**

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Primary Examiner—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Benjamin Aaron Adler

(57) **ABSTRACT**

The present invention describes for the first time the design and synthesis of a soluble tumor-directed paclitaxel prodrug which may establish a new mode of utilization of the taxane class of anticancer agents in cancer therapy.

14 Claims, 8 Drawing Sheets

US006476242B1

(12) **United States Patent**
Kingston et al.

(10) **Patent No.: US 6,476,242 B1**
(45) **Date of Patent: Nov. 5, 2002**

(54) **2-AROYL-4-ACYL PACLITAXEL (TAXOL) ANALOGS**

(75) Inventors: **David George Ian Kingston**, Blacksburg, VA (US); **Mahendra Devichand Chordia**, Charlottesville, VA (US); **Prakash G. Jagtap**, Blacksburg, VA (US); **John Kadow**, Wallingford, CT (US)

(73) Assignees: **Bristol-Myers Squibb Company**, Princeton, NJ (US); **Virginia Tech Intellectual Properties, Inc.**, Blacksburg, VA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/223,193**

(22) Filed: **Dec. 30, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/070,234, filed on Dec. 31, 1997.

(51) **Int. Cl.**[7] **C07D 305/14**
(52) **U.S. Cl.** **549/510**; 549/511
(58) **Field of Search** 549/510, 511

(56) **References Cited**

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Primary Examiner—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Fitzpatrick, Cella, Harper & Scinto

(57) **ABSTRACT**

2-debenzoyl-4-deacetyl paclitaxel, antineoplastic analogs thereof and intermediates are taught, as well as the formation of the compound, analogs and intermediates. The compound, analogs and intermediates may be used to form pharmaceutical compositions having anti-neoplastic activity. Further, the compound, analogs and intermediates may be used to treat cancer when applied in an effective amount by means such as a pharmaceutical composition.

3 Claims, 3 Drawing Sheets

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
25 January 2001 (25.01.2001)

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(10) International Publication Number
WO 01/05779 A2

(51) International Patent Classification[7]: C07D 305/00

(21) International Application Number: PCT/US00/19524

(22) International Filing Date: 17 July 2000 (17.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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(74) Agents: **COOPER, Rod, C.** et al.; Sidley & Austin, 717 North Harwood, Dallas, TX 75201 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05779 A2

(54) Title: METHOD OF DESIGNING TUBULIN POLYMERIZATION STABILIZERS

(57) Abstract: A method for designing paclitaxel alternative compounds which stabilize the tubulin polymerization process has been found. These compounds in solution possess steric conformational properties of natural paclitaxel and are capable of binding to the tubulin protein at the same site where paclitaxel is known to bind. The compounds of the present invention stabilize tubulin polymerization in a way that is mechanistically equivalent to activity mechanism of paclitaxel. The compounds of the present invention have increased solubility, simpler synthesis, and the possibility for specificity and optimization due to the combinatorial reactions over natural paclitaxel.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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(10) International Publication Number
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(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US00/15544

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(26) Publication Language: English

(30) Priority Data:
60/137,549 4 June 1999 (04.06.1999) US

(71) Applicants and
(72) Inventors: AU, Jessie, L.-S. [US/US]; 2287 Palmleaf Court, Columbus, OH 43235 (US). WIENTJES, Guillaume [NL/US]; 2287 Palmleaf Court, Columbus, OH 43235 (US).

(74) Agents: LAURO, Peter, C. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/74667 A2

(54) Title: METHODS AND COMPOSITIONS FOR MODULATING DRUG ACTIVITY THROUGH TELOMERE DAMAGE

(57) Abstract: The invention provides methods and compositions for modulating the activity of therapeutic agents for the treatment of a cancer by administering one or more agents that (either alone or in combination) induces telomere damage and inhibits telomerase activity in the cancer cell. The method initially uses, e.g., a telomere damage-inducing agent such as paclitaxel, and a telomerase inhibitory agent such as AZT. The invention also provides methods for identifying other agents with telomere damage-inducing activity and/or telomerase inhibitory activity (as well as and compositions having such activity), for use in the treatment of cancer.

US006197981B1

(12) **United States Patent**
Liu

(10) **Patent No.: US 6,197,981 B1**
(45) **Date of Patent: Mar. 6, 2001**

(54) **PROCESS FOR CONVERTING 9-DIHYDRO-13-ACETYLBACCATIN III INTO TAXOL AND DERIVATIVES THEREOF**

(75) Inventor: **Jian Liu**, 470 Cherry Avenue, Fredericton, New Brunswick E3A 5N9 (CA)

(73) Assignee: **Jian Liu**, Fredericton (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/423,049**

(22) PCT Filed: **May 1, 1998**

(86) PCT No.: **PCT/CA98/00401**

§ 371 Date: **Nov. 1, 1999**

§ 102(e) Date: **Nov. 1, 1999**

(87) PCT Pub. No.: **WO98/50378**

PCT Pub. Date: **Nov. 12, 1998**

(30) **Foreign Application Priority Data**

May 1, 1997 (CA) 2204197

(51) **Int. Cl.**[7] **C07D 305/14**

(52) **U.S. Cl.** **549/510**; 549/511

(58) **Field of Search** 549/510, 511

(56) **References Cited**

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* cited by examiner

Primary Examiner—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Paul S. Sharpe; Marks & Clerk

(57) **ABSTRACT**

Process for preparing taxol, baccatin III and 10-deacetylbaccatin III by oxidation of 9-dihydro-13-acetylbaccatin III.

16 Claims, No Drawings

US005723634A

United States Patent [19]

Holton

[11] Patent Number: 5,723,634

[45] Date of Patent: *Mar. 3, 1998

[54] **METAL ALKOXIDE COMPOUNDS**

[75] Inventor: **Robert A. Holton**, Tallahassee, Fla.

[73] Assignee: **Florida State University**, Tallahassee, Fla.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,229,526.

[21] Appl. No.: **483,309**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 314,532, Sep. 28, 1994, Pat. No. 5,466,834, which is a continuation-in-part of Ser. No. 949,107, Sep. 22, 1992, abandoned, which is a continuation-in-part of Ser. No. 863,849, Apr. 6, 1992, abandoned, which is a continuation-in-part of Ser. No. 862,955, Apr. 3, 1992, abandoned, which is a continuation-in-part of Ser. No. 763,805, Sep. 23, 1991, abandoned.

[51] **Int. Cl.**[6] **C07D 305/14**

[52] **U.S. Cl.** **549/510**; 549/511

[58] **Field of Search** 549/510, 511

[56] **References Cited**

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Palomo et al. "Highly Stereoselective Synthesis of α-Hydroxy β-Amino Acids Through β-Lactams: Application to the Synthesis of the Taxol and Bestatin Side Chains and Related Systems" Tetrahedron Let., vol. 31, No. 44 (1990) p. 6429.

(List continued on next page.)

Primary Examiner—Ba K. Trinh

Attorney, Agent, or Firm—Senniger, Powers, Leavitt & Roedel

[57] **ABSTRACT**

A process for preparing N-acyl, N-sulfonyl and N-phosphoryl substituted isoserine esters in which a metal alkoxide is reacted with a β-lactam.

28 Claims, No Drawings

OTHER PUBLICATIONS

Samaranayake et al. "Modified Taxols. 5. Reaction of Taxol With Electrophilic Reagents and Preparation of a Rearranged Taxol Derivative with Tubulin Assembly Activity" Journal of Organic Chemistry. vol. 56 (1991) pp. 5114–5119.Schultz et al. "Synthesis of New N–Radicals of Tetrazan–1–yl" Chemical Abstracts. vol. 108. No. 37298C (1988) p. 581.

Wani et al. "Plant Antitumor Agents. VI. The Isolation and Structure of Taxol, A Novel Antileukemic and Antitumor Agent From *Taxus brevifolia*" Journal of American Chemical Soc. vol. 93, No. 9 (May 5, 1971) pp. 2325–2327.

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US005670663A

United States Patent [19]

Durzan et al.

[11] Patent Number: 5,670,663

[45] Date of Patent: Sep. 23, 1997

[54] **RECOVERY OF TAXANES FROM CONIFERS**

[75] Inventors: **Don J. Durzan**; **Frank Ventimiglia**, both of Davis, Calif.

[73] Assignee: **Regents of the University of California**, Oakland, Calif.

[21] Appl. No.: **601,367**

[22] Filed: **Feb. 14, 1996**

[51] **Int. Cl.**[6] **C07D 305/14**

[52] **U.S. Cl.** **549/332**; 549/510; 560/248

[58] **Field of Search** 549/510, 332; 560/248

[56] **References Cited**

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5,547,866 8/1996 Durzan et al. .

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Primary Examiner—Christina Y. Chan

Assistant Examiner—Emma Cech

Attorney, Agent, or Firm—Townsend and Townsend and Crew LLP

[57] **ABSTRACT**

The present invention provides new sources of taxanes and other metabolites from members of the order Coniferales that are not in the genus Taxus.

11 Claims, No Drawings

US006025507A

United States Patent [19]

Klar et al.

[11] **Patent Number: 6,025,507**

[45] **Date of Patent: Feb. 15, 2000**

[54] **BORNEOL DERIVATIVES, METHODS OF MANUFACTURING THEM, AND THEIR PHARMACEUTICAL USE**

[75] Inventors: **Ulrich Klar; Hernamm Graf; Günter Neef; Siegfried Blechert**, all of Berlin, Germany

[73] Assignee: **Schering Aktiengesellschaft**, Berlin, Germany

[21] Appl. No.: **08/894,180**

[22] PCT Filed: **Feb. 19, 1996**

[86] PCT No.: **PCT/DE96/00297**

§ 371 Date: **Aug. 28, 1998**

§ 102(e) Date: **Aug. 28, 1998**

[87] PCT Pub. No.: **WO96/25392**

PCT Pub. Date: **Aug. 22, 1996**

[30] **Foreign Application Priority Data**

Feb. 17, 1995 [DE] Germany 195 06 885

[51] **Int. Cl.**[7] **C07D 303/16**; C07C 271/22; A61K 31/325; A61K 31/335

[52] **U.S. Cl.** **549/543**; 560/23; 560/29; 514/475; 514/507

[58] **Field of Search** 549/543; 560/23, 560/29; 514/507, 475

[56] **References Cited**

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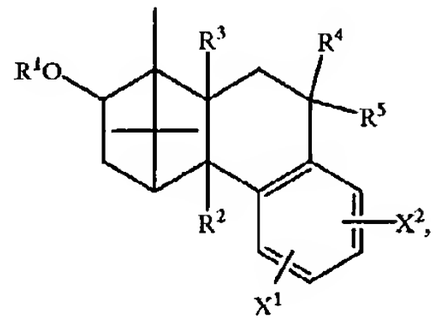
4416374	11/1995	Germany .

Primary Examiner—Ba K. Trinh
Attorney, Agent, or Firm—Millen, White, Zelano & Branigan, P.C.

[57] **ABSTRACT**

Borneol derivatives of formula I



I

in which R^1 to R^5 and X^1 to X^2 are defined in the specification, and the method of making the same.

15 Claims, No Drawings

A1

6. The method of Claims 1, 2, 3 or 4, wherein said known anti-tumor composition is paclitaxel.

7. A method for designing a paclitaxel alternative composition, which alternative composition has a central skeleton structure composed of single or multiple ring groups which hold multiple functional groups in a fairly rigid alignment, said central skeleton structure having first, second, and third side chains;

wherein said first side chain is connected to said central skeleton with a carbonyl group at a distance of about 1.5 to 5.5 Angstroms from said central skeleton;

wherein said second side chain places an sp^3 oxygen atom at a distance of about 4.5 to 7.5 Angstroms from the skeleton and about 9 to 11 Angstroms from the carbonyl oxygen of said first side chain;

wherein said third side chain is placed in an energetically accessible conformation that places an aromatic ring in a location that is simultaneously about 4 to 6 Angstroms from a substitute for hexene and about 8 to 10 Angstroms from the oxygen in said second side chain, said third side chain selected to mimic the steric and binding properties of the C2 ester in paclitaxel;

said method comprising using molecular modeling software on a computer to design said alternative composition.

PCT 7/15/00
Prov. 7/15/99

8. The method of Claim 7, wherein said alternative composition further comprises one or more bulking groups and wherein said bulking groups increase the size of said composition to mimic the overall size and shape of the paclitaxel molecule.

9. The method of Claim 7, wherein said first side chain is selected and positioned to mimic the isoserine group in taxane.

10. The method of Claim 7, wherein said sp^3 oxygen is positioned in space to simulate the position of the oxetane ring of paclitaxel.

A2

11. The method of Claims 7, 8, 9 or10, further comprising synthesizing said alternative composition.

L5 ANSWER 67 OF 343 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on Full Text

STN

AN 1998:407105 BIOSIS

DN PREV199800407105

TI Antitumor activity of **paclitaxel** (taxol) analogues on MDR-positive human cancer cells.

AU Distefano, M.; Scambia, G.; Ferlini, C.; Gallo, D.; De Vincenzo, R.; Filippini, P.; Riva, A.; Bombardelli, E.; Mancuso, S. [Reprint author]

CS Dep. Obstet. Gynecol., Catholic Univ. Sacred Heart, Lgo A. Gemelli, I-00168 Rome, Italy

SO Anti-Cancer Drug Design, (July, 1998) Vol. 13, No. 5, pp. 489-499. print. CODEN: ACDDEA. ISSN: 0266-9536.

DT Article

LA English

ED Entered STN: 21 Sep 1998
Last Updated on STN: 5 Nov 1998

AB A series of newly developed **paclitaxel** analogues have been tested for their growth inhibitory activity on two human breast cancer cell lines, one of which expresses the MDR (multidrug resistance) phenotype. **Paclitaxel** (taxol) was used as a reference compound. Three new classes of **taxanes** were analyzed: the cephalomannine compounds, the pyrazoline derivatives and the seco-derivatives. Our results demonstrated an increased antiproliferative activity of pyrazoline derivatives on drug-resistant cancer cells with respect to **paclitaxel**. These compounds were able to block MDR-bearing MCF-7 ADRr cells in the G2/M phase of cell cycle and, consequently, induce programmed cell death. In keeping with the antiproliferative effects, cells treated with **paclitaxel** derivatives showed a more pronounced cell cycle arrest than the parent compound **paclitaxel**. Also, apoptotic cell death, calculated as a percent of DNA fragmentation, occurred to a greater extent in cells exposed to pyrazoline derivatives. The development of new **paclitaxel** analogues with greater antitumor activity on MDR-positive cells may be useful in selecting new **taxanes** effective on resistant tumors.

L5 ANSWER 65 OF 343 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS
Full Text
RESERVED. on STN
AN 97080954 EMBASE
DN 1997080954
TI From serendipity to **design**: The evolution of drug development in oncology.
AU Peereboom D.M.
CS Dr. D.M. Peereboom, Dept. of Hematology/Oncology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States
SO Cleveland Clinic Journal of Medicine, (1997) 64/3 (155-163).
Refs: 51
ISSN: 0891-1150 CODEN: CCJMEL
CY United States
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Although screening of natural products remains the major method of discovering new anticancer drugs, newer techniques of rational drug **design**, **computer**-aided drug **design**, and combinatorial synthesis promise to broaden the scope of compounds available for screening. Recent changes in Food and Drug Administration rules allow for accelerated approval of drugs for treating cancer and other life-threatening illnesses, although the three-phase process of clinical trials remains largely unchanged.

L5 ANSWER 31 OF 343 CAPLUS COPYRIGHT 2004 ACS on STN
Full Text
AN 1996:88388 CAPLUS
DN 124:164106
TI Taxoids: a new class of antimitotic compounds
AU Guenard, Daniel; Gueritte-Voegelein, Francoise; Lavelle, Francois
CS Inst. Chimie Substances Naturelles, Cent. Natl. de la Rech. Scientifique, Gif-sur-Yvette, 91198, Fr.
SO Current Pharmaceutical Design (1995), 1(1), 95-112
CODEN: CPDEFP; ISSN: 1381-6128
PB Bentham Science Publishers
DT Journal; General Review
LA English
AB A review with 165 refs. **Paclitaxel** (Taxol®) and docetaxel (Taxotere®) are the first representatives of taxoids, a new class of antitumor compds. These two taxoids are clin. active against breast, ovarian and lung cancers. Taxoids are highly complex diterpenoids from natural origin. Preclin. and clin. developments have been made possible after a long and sustained chem. effor : **paclitaxel** is extd. from the barks of the Pacific yew tree Taxus brevifolia whereas docetaxel is prepd. by hemisynthesis starting from 10-deacetyl-baccatin III, a non cytotoxic precursor found in the needles of the European yew Taxus baccata. These two drugs are active in various in vitro and in vivo preclin. models (cell lines, cloning of human tumor stem cells, murine grafted tumors, human xenografts). Taxlids constitute anew class of antimitotic agents different from vinca-alkaloids: on the one hand, **paclitaxel** and docetaxel can be considered as inhibitors of the reaction of depolymn. of microtubules into tubulin; on the other hand, vinca-alkaloids inhibit the reaction of polymn. of tubulin into microtubules. An active **program** of medicinal chem. is done in various pharmaceutical and academic Institutions with two objectives: knowledge of structure-activity relationships and selection of new candidates for clin. trials. With the taxoid series, a variety of analogs have been prepd. for their antitubulin and biol. properties. Concerning the tubulin binding, some important structure activity relationships have been proposed. In this review the contribution of each functional group of docetaxel will be discussed following the evolution of antitubulin activity, going from docetaxel to taxoids possessing the min. requirement of recognition by tubulin. The conformation of docetaxel and analogs will be compared taking into account the contribution and relevance of x-rays, NMR and mol. **modeling** studies in detg. the mol. shape of active and inactive compds.

AN 1996:414636 CAPLUS
TI Synthesis and formulation of a lipophilic prodrug of **paclitaxel** for liposomal delivery.
AU Ansell, Steven M.; Wheeler, Jefferey J.; Kojic, Liljana
CS Inex Pharmaceuticals Corp., Vancouver, BC, V6P 6P2, Can.
SO Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (1996), MEDI-048 Publisher: American Chemical Society, Washington, D. C. CODEN: 63BFAF
DT Conference; Meeting Abstract
LA English
AB A lipophilic **paclitaxel** prodrug, protax-3, was synthesized and formulated in egg phosphatidylcholine (EPC) liposomes. The prodrug was shown to be cytotoxic at similar concns. (<100nM range) as **paclitaxel** in free drug cytotoxicity assays. The exchange kinetics were detd. for a 4% formulation with EPC in the presence of serum using a **modeling system**. Similar kinetics were obsd. in vitro and in vivo using a 4% formulation with EPC and 5% N-(2'-(ω-methoxypolyethyleneglycol)succinoyl)-1,2-distearoylphosphatidyl-ethanolamine (MePEGS-2000-DSPE), thereby establishing the validity of the exchange model. The protax-3: EPC:MePEGS-2000-DSPE and EPC:MePEGS-2000-DSPE liposome formulations showed in vivo clearance properties comparable to conventional liposomes.

L5 ANSWER 59 OF 343 MEDLINE on STN
Full Text
AN 1998021286 MEDLINE
DN PubMed ID: 9379451
TI Conformational studies of **paclitaxel** analogs modified at the C-2' position in hydrophobic and hydrophilic solvent **systems**.
AU Moyna G; Williams H J; Scott A I; Ringel I; Gorodetsky R; Swindell C S
CS Department of Chemistry, Texas A&M University 77843-3255, USA.
NC GM32596 (NIGMS)
SO Journal of medicinal chemistry, (1997 Sep 26) 40 (20) 3305-11.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971110

AB The conformations of two **paclitaxel** analogs modified at the C-2' position, 2'-deoxypaclitaxel and 2'-methoxypaclitaxel, were studied in hydrophobic and hydrophilic solvent **systems** by a combination of NMR spectroscopy, CD measurements, and molecular **modeling**. Both analogs have hydrophobic and hydrophilic conformations that resemble those of **paclitaxel** itself in the same media. Since the two have diminished biological activities in a number of bioactivity assays and the hydrogen-bonding capability of the 2'-hydroxyl group has been eliminated, we postulate that this group is involved in hydrogen bonding with tubulin and plays an important role in molecular recognition. The results of this study are in agreement with our earlier report on **paclitaxel** 2'-acetate, an analog in which the 2'-hydroxyl group hydrogen-bonding capacity has also been eliminated.